IFW/DAC

Attorney's Docket No.: 10845-044001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicant | : Huw M. Nash, et al. | Art Unit | : Unknown |
| Serial No. | : 10/806,758 | Examiner | : Unknown |
| Filed | : March 22, 2004 | | |
| Title | : METHOD OF SCREENING FOR TARGET LIGANDS | | |

**Mail Stop Missing Parts**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION UNDER 37 CFR 1.47(a) TO PROSECUTE APPLICATION ON BEHALF OF EIGHT SIGNING AND ONE NON-SIGNING INVENTOR, DANIEL L. FLYNN

Inventors, Huw M. Nash, Keith Mason, Ciamac Moallemi, Edward Wintner, Michael Kelly, Steve Adams, Zhongli Zheng, and Greg Makara, through their assignee Neogenesis Pharmaceuticals, Inc., ("Neogenesis") freely petition to prosecute the above referenced application.

The pertinent facts are set forth below. Proof of these facts in submitted herewith in the attached statement of facts as declared by David W. Skinner, Esq., counsel for Neogenesis.

Daniel L. Flynn, Ph. D. ("Dr. Flynn"), one of nine inventors of the above referenced patent application, has refused to sign the combined declaration and power of attorney presented to him for the above referenced application. The above referenced application and combined declaration and power of attorney were presented to Dr. Flynn on July 7, 2004, and copies of referenced provisional applications were further presented to Dr. Flynn on July 13, 2004. After reviewing these patent applications, Dr. Flynn, responding by letter, refused to execute the declaration for the above referenced patent application.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

November 15, 2004
Date of Deposit

Linda M. White
Signature

Linda M. White
Typed or Printed Name of Person Signing Certificate

11/22/2004 FFANAIA2 00000038 10806758

01 FC:1460 130.00 OP

The last known addresses of Dr. Flynn are provided below:

| **Home** | **Work** |
|---|---|
| Daniel L. Flynn, Ph.D. | Daniel L. Flynn, Ph.D. |
| 4165 Blackjack Oak Drive | Deciphera Pharmaceuticals |
| Lawrence, KS 66047 | 1505 Wakarusa Drive |
| | Lawrence, KS 66047-1803 |

Enclosed is a check for the fee set forth in §1.17(h). Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: November 15, 2004

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Attorney's Docket No.: 10845-044001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Huw M. Nash, et al.
Serial No. : 10/806,758
Filed : March 22, 2004
Title : METHOD OF SCREENING FOR TARGET LIGANDS

Art Unit : Unknown
Examiner : Unknown

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Alexandria, VA 22313-1450

STATEMENT OF FACTS TO ACCOMPANY PETITION UNDER 37 CFR 1.47(a)

To the best of my information and belief, formed after reasonable inquiry:

Daniel L. Flynn, Ph.D. was formerly employed by Neogenesis Pharmaceuticals, Inc. ("Neogenesis").

I sent a copy of the above referenced application to Daniel L. Flynn, Ph. D. ("Dr. Flynn") at his current work address on July 7, 2004, along with a combined declaration and power of attorney and an assignment for his review and execution.

On July 8, 2004, Dr. Flynn replied by letter asking for copies of the provisional patent applications referenced in the above application.

In response, I sent Dr. Flynn copies of the two provisional applications referenced in the above application on July 13, 2004.

On July 29, 2004, Dr. Flynn responded by letter, stating that he had reviewed the above application, as well as the referenced provisional applications. He refused to execute either the combined declaration and power of attorney or the assignment. A copy of this letter is attached herewith as Exhibit A.

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Linda M. White
Signature

Linda M. White
Typed or Printed Name of Person Signing Certificate

In a subsequent letter dated October 21, 2004, Dr. Flynn wrote a letter to Neogenesis providing additional rationale for refusing to execute the declaration for the above application. A copy of this letter is attached herewith as Exhibit B.

The remaining eight joint inventors signed a combined declaration and power of attorney, together with an assignment to Neogenesis.

For the record, Neogenesis contests Dr. Flynn's assertions regarding the patentability of the claimed invention. In view of obligations arising from Dr. Flynn's prior employment by Neogenesis, Neogenesis further contends Dr. Flynn's assertions regarding ownership of his rights in the claimed invention.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that those statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

David W. Skinner, Esq. 11/15/04
David W. Skinner, Esq.
Reg. No. 55,772

Patent Counsel
Neogenesis Pharmaceuticals, Inc.
840 Memorial Drive
Cambridge, MA 02139


July 29, 2004

Daniel L. Flynn, PhD
4165 Blackjack Oak Drive
Lawrence, KS 66047

Mr. David W. Skinner, Esq.
Neogenesis, Inc.
840 Memorial Drive
Cambridge, MA 02139

RE: Neogenesis Patent Application Entitled "Method of Screening for Target Ligands" Filed March 22, 2004, S/N 10/806,758

Dear Mr. Skinner:

As you requested, I have reviewed the above patent application, as well as the earlier provisional applications you forwarded to me. You have asked that I execute certain documents in connection with this application, but at present I cannot do this for reasons explained below.

Surprisingly, the Neogenesis applications contain significant technical information which is clearly my property and that of my company, Deciphera Pharmaceuticals, Inc., and doesn't belong to Neogenesis. Certain information was disclosed to Neogenesis in August, 2002, when Neogenesis was considering an investment in my new company. The Neogenesis officers declined that opportunity, but acknowledged that "the founders are developing some insights whose exploitation lies outside the NeoGenesis mainstream agenda... and the Deciphera founders will be best able to achieve their personal objectives by pursuing their interests outside Neogenesis." Therefore, the information that I and Pete Petillo disclosed to the Neogenesis officers was our property and lay outside of Neogenesis' agenda and sphere of technology.

I note that many of the claims of this utility application utilize Neogenesis' ALIS screening platform using mass spectrometry and mass encoded libraries. In an effort to amicably resolve this situation and avoid legal entanglement, it occurred to me that if Neogenesis would agree to amend its application so that *all* claims are similarly limited to screening with their mass spectrometry and mass encoded libraries, then I would be prepared to sign the documents. By putting your claims in this posture, this would sufficiently differentiate Neogenesis' technology from the technology that is exclusively ours.

If Neogenesis is willing to accept this proposal of amended claims, forward to me a letter of agreement to this effect. I will discuss this with our counsel, and hopefully this will lead to a resolution.

I am aware that there is some urgency in bringing this matter to closure, and trust that we can resolve this issue within the next 10 days.

Very truly yours,

Daniel L. Flynn, PhD

October 21, 2004

Daniel L. Flynn, PhD
4165 Blackjack Oak Drive
Lawrence, KS 66047

Mr. David W. Skinner, Esq.
Neogenesis, Inc.
840 Memorial Drive
Cambridge, MA 02139

Dear Mr. Skinner:

I have carefully reviewed again the patent application which you sent to me entitled "Method of Screening for Target Ligands", for which I have been listed as a co-inventor. Upon only a cursory review of three previously published papers, I have determined that the majority of claims put forth in this application are explicitly taught in three 2002 publications and that the claims represent an amalgam of their collective teaching. These references site a new DFG-out conformation pocket that can be used for the design of allosteric inhibitors of kinases. The publication dates of these references predate the filing of the earlier Neogenesis provisional application.

- Schlindler *et al* (*Science* (2000) 289: 1938)
- Pargellis *et al (Nature Structural Biology* (2002) 9: 268)
- Regan *et al* (*Journal of Medicinal Chemistry,* (2002) 45: 2994)

I do not know who assembled the compilation of claims of the Neogenesis provisional application, but from my perspective it appears that someone may have read these three papers and essentially drafted a provisional w/claims based on the explicit teachings from these three references. My analysis is summarized below. I think if you only casually read the Pargellis, Schlindler, and Regan references sited above, you will clearly see what was done. There is little or nothing inventive here. Certainly not beyond Claim 22. Claims 39 and 52 might possibly be novel if you were to restrict them to the use of mixtures of a mass-encoded library in mass spectrometry affinity screening. The majority of the scope of most claims has been explicitly taught in the three noted references. I do not want to be included as an inventor on this patent as written, as there is nothing inventive in the bulk of the application. I would be happy to sign as a co-inventor if the claims are restricted to what was not known in the prior art previous to the filing date of this provisional application. Specifically, I would be prepared to execute the application and the assignment to Neogenesis if all of the claims of the application not completely anticipated by the prior art would be amended to include the step of mass spectrometry screening as now set forth in some of the claims. My inventive participation on the kinase inhibitor research at Neogenesis was indeed restricted to the application of mass spectrometry-based screening to identify kinase inhibitors. Additionally, I would require an undertaking on the part of Neogenesis that the claims throughout the prosecution remain limited in this respect, i.e., that the claims would not hereafter be broadened beyond the mass spectrometry-based screening limitation.

Sincerely,

Daniel L. Flynn, PhD

**Summary analysis of claims and recommendations for their restriction.**

Claim 23 is not novel. Schlindler *et al* (*Science* (2000) 289: 1938) teaches that one can compare the allosteric site occupied by gleevec as it inhibits abl kinase with the known 3 dimensional structure of other Src type kinases and the insulin receptor kinase and make predictions about design based on such comparisons. Quotes from this paper include the following: "The striking similarity between the conformation of the activation loop and the manner in which peptide substrates bind to tyrosine kinases suggest that the loop (of Abl kinase) is in a natural auto-inhibitory conformation (Fig 1D). Comparison of the catalytic domain of Abl and inactive IRK (insulin receptor kinase) shows that the central part of the activation loop in both kinases occludes the mouth of the catalytic domain and interferes with the productive binding of peptide substrates in a similar manner (fig. 1D). Although Tyr393 is positioned exactly as in a substrate peptide, the kinase domain is not in a conformation which is competent for phosphate transfer to the tyrosine, since the inward movement of the activation loop is coupled to displacement of the Asp-Phe-Gly motif away from the active conformation in both kinases [Asp 381 points away from the active site (Fig 1C)]." Furthermore, the comparative structures are actually co-illustrated in Figure 1D. Comparisons of these pockets, as taught by Schlindler allow one to identify the allosteric site and design inhibitors based on that analysis.

It not surprising that the very structures that are compared in this Schlindler reference are among the first three structures delineated in Claims 29 and 30. Indeed, the Schlindler reference actually generates and compares these same structures in the body of his paper.

Furthermore, Pargellis et al (*Nature Structural Biology* (2002) 9: 268) describe BIRB-796, an allosteric inhibitor of a different kinase, the serine/threonine kinase p38-alpha. This paper explicitly teaches that this binding mode is allosteric. The title of the paper is even indicative as to its content: "Inhibition of p38 MAP kinase by utilizing a novel allosteric binding site". Furthermore, in this paper Pargellis teaches "To our knowledge, this is the first time that the DFG-out conformation has been observed in a protein Ser/Thr kinase. In contrast, the DFG-out conformation seems to be more stable in protein Tyr kinases. The inactive insulin receptor tyrosine kinase exists almost exclusively in the DFG-out conformation , which also interferes with the binding of ATP. Recently the Abl tyrosine kinase in complex with the Novartis inhibitor, STI-571, was observed in the DFG-out conformation. The binding mode of the STI inhibitor bears resemblance to the diarylurea compounds described here. However, the Phe pocket is not fully occupied by the STI inhibitor. **Our structural and solution studies suggest that the conformational variability of the DFG motif may be a general phenomenon in the protein Ser/Thr and Tyr kinases that can be utilized in the design and development of new selective inhibitors against protein kinases.**"

It is not surprising that the very structures that are sited in this Pargellis reference are among the other structures delineated in Claim 28. Indeed, the Pargellis reference compares and constrasts the 1kv1 and 1kv2 allosteric pockets with the 1iep, 1fpu, and 1irk structures.

The dependent claims 24-38, which refer back to Claim 23 are therefore not novel. **Claim 33 even identifies this allosteric site as being the DFG motif clearly taught and compared in the above sited references.**

The next section of claims, based on the independent Claim 39, are a reconstitution of Claim 23 with the added process steps of providing a mixture of compounds (step d) and identifying ligands for the allosteric site by affinity screening against the kinase (step e). This claim is also not novel and fully anticipated based on the published literature at the time of the writing of this

provisional patent. The teachings of the Schlindler reference and the Pargellis reference describe using and comparing structures of this allosteric site in the design of kinase inhibitors. **Furthermore, the Pargellis reference explicitly teaches the use of affinity screening to identify ligands.** They used a fluorescence affinity screen based on the flouroprobe molecule SKF 86002. Hence, Claim 39 has already been fully disclosed in the Pargellis reference in terms of 1) design, and 2) use of an affinity screen. **Moreover, Regan *et al* (*Journal of Medicinal Chemistry*, (2002) 45: 2994) teach the use of affinity screening using mixtures of compounds.** Tables 2 and 4 site examples of the use of racemic mixtures in a flourescence affinity assay to identify ligands for p38-alpha kinase. The only viable avenue for Neogenesis to retain novelty of Claim 39 is to restrict the process to involve the screening of mixtures in a mass-encoded library by use of mass spectrometry affinity screening.

By analogy, the dependent Claims 40-47, which refer to the independent Claim 39 are also not novel, or they are anticipated.

Independent Claim 49 and dependent Claims 50-51 are not novel and are also anticipated by the collection of references from Schlinder, Pargellis, and Regan.

Claim 52 as a whole process of steps (a) through (i) may be novel, but it would depend on the patent office not siting previously published Neogenesis patents describing mass-encoded libraries (steps d,e,f,g) and their use in mass spectrometry affinity screening. The other steps (a,b,c,h and i) are fully anticipated or are explicitly taught in the Schlindler, Pargellis, and Regan references.

Claim 53 is fully anticipated or explicitly taught in the references provided by Schlindler, Pargellis, and Regan. I would only recommend keeping Claim 52. Claim 52 does retain the novelty of using mass-encoded libraries in mass spectrometry affinity screening.

Regarding dependent claims 54-59, they are likely to be rejected as written. I would recommend having these claims only refer to Claim 52, and delete their referral to Claims 39, 41, 42, 49, and 53. Again, these other claims are not novel and will undoubtedly be rejected based on the Schlindler, Pargellis, and Regan references.

By analogy, the only novel aspects of dependent Claims 60-61 would be to limit their referral back to claims 13 and 52, and delete their referral back to Claims 23, 39, 49, or 53.

Claims 62 and 63 are not novel. The Pargellis paper and Regan paper teach that BIRB-796 and related analogs bind to an allosteric site remote from the ATP pocket, and furthermore, that this site is the allosteric site present when a DFG motif of the kinase is in a DFG-out position. **Furthermore, the paper explicitly teaches that the inhibitor keeps ATP from binding by occluding the ATP binding pocket indirectly, and that such indirect inhibition of the ATP pocket leads to inhibition of functional enzyme activity by performing a kinase assay in the presence or absence of the inhibitor. See the Pargellis paper, Methods section: binding studies (page 271).**

Claim 64 codifies what has already been published on two different kinases by two different research groups and reported in the 2002 literature. The pocket subtended by step c of this claim is the same pocket taught by the Pargellis reference for the DFG-motif out conformation pocket of p38-alpha kinase and by the Schlindler reference for the DFG-motif out conformation of abl kinase. Thus, Claim 64 is anticipated by the combination of the Pargellis and Schlindler references.

Claim 65 is fully and explicitly taught separately and in composite by the Pargellis and the Schlindler references.

Claim 66 could be retained if it referred only to a modified independent claim 52 restricted to the use of mass encoded library mixtures and mass spectrometry affinity screening.

Dependent claims 67-69 are not novel as they refer back to Claim 65.

**Claim 70 is not novel. Such allosteric inhibitors of several kinases already exist. The Pargellis and the Schlindler papers alone refer to such derived inhibitors of p38-alpha kinase, p38-beta kinase, jnk kinase, abl kinase, PDGFR kinase, and c-Kit kinase. Dependent claims 71-87 are therefore not novel.**

Claim 88 is not novel. The induced concave pocket is explicitly taught in the Pargellis, Regan, and Schindler references. Dependent Claims 89-90 are also not novel. **Moreover, amino acids 104-109 of PDB accession code 1kv2 are explicitly taught as forming a pocket in Figure 3 of the Pargellis paper (see page 269). By analogy, claim 90 also is not novel.**